Motor intention as a trigger for fear of movement-related pain: An experimental cross-US reinstatement study

Ann Meulders[1, 2], Ann Rousseau[3], & Johan W.S. Vlaeyen[1, 2, 4]

[1]Research Group on Health Psychology, University of Leuven, Leuven, Belgium

[2]Center for Excellence on Generalization Research in Health and Psychopathology, University of Leuven, Leuven, Belgium

[3]School for Mass Communication Research, University of Leuven, Leuven, Belgium

[4]Department of Clinical Psychological Science, Maastricht University, The Netherlands

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Correspondence concerning this article should be addressed to Ann Meulders, Ph.D, Department of Psychology, University of Leuven, Tiensestraat 102, box 3726, 3000 Leuven, Belgium. E-mail: ann.meulders@ppw.kuleuven.be, T: +32 (0)16 32 60 38, F: +32 (0)16 32 61 44.

Abstract

Using a voluntary joystick movement task with arm movements as conditioned stimuli (CSs) a and a painful electrocutaneous stimulus as an unconditioned stimulus (pain-US), we investigated whether 1) the intention to perform a painful movement would elicit pain-related fear in healthy participants, 2) a non-painful but aversive sound-US (i.e. human scream) could induce cross-US reinstatement. . All groups (same-US/different-US/no-US) received acquisition and extinction with the pain-US. During reinstatement, the same-US group received two unsignaled pain-USs, the different-US group received two unsignaled sound-USs and the no-US group did not receive any stimulus presentations. Next, we tested the return of fear (fear and US-expectancy ratings and startle eyeblink responses) in all groups. Uncoupling motor intention and action led to successful inhibition of pain-related fear elicited by merely thinking about a painful movement as compared to previous study results in which motor intention was always coupled with motor action. The different-US group showed a differential cross-US reinstatement effect in the pain-US expectancy ratings . However, this effect failed to materialize in the fear ratings and startle responses. Taken together, we found partial support for the hypothesis that reinstatement experiences might foster the acquisition of new fears rather than reinstating old fears.

1. Introduction

According to the current fear-avoidance models pain-related fear plays a pivotal role in the development of chronic musculoskeletal pain and disability (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012; Vlaeyen & Linton, 2000, 2012). Contemporary models of associative learning offer a rich conceptual framework to shed light on the origins, maintenance and treatment of human fear and anxiety (Craske, Hermans, & Vansteenwegen, 2006; Lovibond, 2011; Mineka & Zinbarg, 2006). In particular, the human fear conditioning paradigm has been employed extensively as a laboratory model to investigate the development and treatment of fears and phobias (Craske et al., 2006). Most of the fear conditioning research in the anxiety literature used exteroceptive conditioned stimuli (CSs) such as auditory (e.g. tone) or visual (e.g. geometrical figure) stimuli. Musculoskeletal chronic pain, however, is characterized primarily by fear of movement/(re-)injury which is associated with avoidance of feared activities and movements in turn leading to increased pain disability (Vlaeyen & Linton, 2000, 2012). To capture the essence of the prototypical fear of movement-related pain as frequently observed in patients with musculoskeletal pain in a controlled experimental setting, we developed a *proprioceptive fear conditioning paradigm* using joystick arm movements as conditioned stimuli (CSs) and a painful electrocutaneous stimulus as the unconditioned stimulus (pain-US) (Meulders, Vansteenwegen, & Vlaeyen, 2011). Previous research using this voluntary joystick movement paradigm not only demonstrated acquisition, but also generalization (Meulders, Vandebroek, Vervliet, & Vlaeyen, 2013; Meulders & Vlaeyen, 2013a), extinction (Meulders & Vlaeyen, 2012) and return of fear of movement-related pain (Meulders & Vlaeyen, 2013b; Volders, Meulders, De Peuter, Vervliet, & Vlaeyen, 2012) in healthy individuals. Interestingly, a recent study has shown that even the *mere intention to perform a painful movement* can start to elicit conditioned fear of movement-related pain in healthy participants (Meulders & Vlaeyen,

2013b). This study employed an adapted version of the voluntary joystick movement paradigm in which participants had to verbally express the direction (i.e. moving the joystick to the left or to the right) they were going to move on each given trial when prompted by the choice signal. After a choice had been made, a variable intention delay was inserted during which participants had to actively stand ready to perform their movement of choice (i.e. motor intention) as quickly and accurately as possible when the starting signal appeared. The results demonstrate that startle eyeblink responses elicited by probes delivered during the intention delay on CS+ trials were higher than those during CS- trials, but this was not the case for the probes delivered during the context alone (ITI; intertrial interval). This study thus confirms that motor intention can function as a covert CS suggesting that actual motor action may not be necessary to elicit pain-related fear instigating the vicious circle of persisting fear, avoidance and pain disability. Although these findings seem obvious, we did not anticipate to find these results in healthy participants. According to modern learning theory, the opposite might be predicted as well, that is, following a componential CS representation view, inhibition of delay (Vogel, Brandon, & Wagner, 2003) would occur in response to the early CS components. More specifically, the motor intention delay can be seen as the early, covert component of the CS and the motor action can be seen as the late, overt component of the CS. Accordingly, the early components will gain inhibitory properties whereas the late components by virtue of the temporal proximity with the US, will gain excitatory properties. We assumed that healthy subjects would learn that the US was never presented unless the movement was actually performed and thus that the mere intention to perform the painful movement was an indicator of safety rather than of danger, which was not the case. A possible explanation might be that there was a perfect contingency between the motor intention and the motor action in that study. Participants knew that they always had to perform their movement of choice, so intention or thinking about the painful movement might

have been entangled with motor preparation and the accompanying motor action. Therefore, the *first aim* of the present study was to investigate the effect of reducing the contingency between motor intention and motor action on fear of movement-related pain during the intention to perform a painful movement . In order to do so, we adjusted the previous study design to an intention delay-inhibition paradigm. This design includes both trials during which the movement of choice has to be executed and trials during which the movement has to be inhibited. We expected that reducing the 100% contingency between motor intention and motor action, would attenuate the fear of movement-related pain elicited during the mere intention to perform the painful movement in healthy participants.

Exposure in vivo has a strong pedigree as one of the most prevailing treatments for decreasing disabling fear and anxiety (Hermans, Craske, Mineka, & Lovibond, 2006; Vervliet, Craske, & Hermans, 2013), and has now been applied in highly fearful patients with chronic pain as well (Bailey, Carleton, Vlaeyen, & Asmundson, 2010; den Hollander et al., 2010). More specifically, in chronic low back pain sufferers, (Boersma et al., 2004; de Jong, Vlaeyen, Onghena, Goossens, et al., 2005; Linton, Overmeer, Janson, Vlaeyen, & de Jong, 2002; Trost, France, & Thomas, 2008; Vlaeyen & Crombez, 1999; Vlaeyen, de Jong, Geilen, Heuts, & van Breukelen, 2001; Vlaeyen, de Jong, Geilen, Heuts, & van Breukelen, 2002; Vlaeyen, De Jong, Onghena, Kerckhoffs-Hanssen, & Kole-Snijders, 2002), complex regional pain syndrome (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005), and post-traumatic neck pain (de Jong et al., 2008) exposure has been proven an effective strategy to mitigate fear levels, associated disability and pain reports.

Despite the initial effectiveness of this treatment, both in anxiety disorders as well as chronic pain, a substantial proportion of treated patients do not remain symptom-free at follow-up but demonstrate partial or full "*return of fear*" at some point after successful treatment (Rachman, 1989). The present study focuses on "*reinstatement*", a phenomenon that

is characterized by recovered conditioned responding after extinction due to exposure to unpredictable US presentations. The reinstatement effect has been well documented primarily in animals (Bouton & Bolles, 1979; Rescorla & Heth, 1975), but during the last two decades research in humans has gained interest. Human fear reinstatement has been reported using verbal fear and US-expectancy measures (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004; Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2007; Dirikx, Vansteenwegen, Eelen, & Hermans, 2009; Hermans et al., 2005), psychophysiological correlates of fear (LaBar & Phelps, 2005; Milad, Orr, Pitman, & Rauch, 2005; Norrholm et al., 2006), as well as behavioral measures of attention (Dirikx et al., 2004; Dirikx et al., 2007; Dirikx et al., 2009; Hermans et al., 2005; Van Damme, Crombez, Hermans, Koster, & Eccleston, 2006). Notwithstanding the increased scientific attention to this topic, important issues regarding the underlying mechanisms of reinstatement and the minimal conditions for its occurrence remain unsettled.

One important issue that might have significant clinical implications concerns whether a US that is qualitatively different than the acquisition US can produce fear reinstatement. Indeed, in many clinical cases the original "*unconditioned stimulus*" is unknown (Hermans et al., 2005). In addition, unrelated negative life events, re-exposure to trauma-related stimuli and stressful periods sometimes aggravate clinical anxiety symptoms, hence the idea has been put forward that reinstatement mechanisms might be at work (Jacobs & Nadel, 1985). In animals, post-extinction presentations of a US that shares the same valence (e.g., foot shock) but is qualitatively different than the acquisition US (e.g., loud noise) can come to increase conditioned responding (Rescorla & Heth, 1975; Storsve, McNally, & Richardson, 2010). Contrary to these findings, post-treatment administration of electrical stimulation did not lead to reinstatement of extinguished phobic fear in spider and snake phobic patients (Rachman & Whittal, 1989). Of course, it is disputable whether an electrical stimulus, serving as a

reinstatement US, is sufficiently powerful to produce a relapse of clinical phobic fear. Therefore, Sokol and Lovibond (Sokol & Lovibond, 2012) wanted to examine this issue in the controlled setting of a human fear conditioning lab using a 2 x 3 factorial design in which reinstatement (same-US, different-US and no-US) and acquisition US (shock vs. loud noise) were manipulated between-subjects. The authors did not only measure skin conductance to tap into the emotional arousal arising from fear and anxiety, but they also focused on more cognitive processes that might be involved in reinstatement. More particularly, they registered US-expectancy ratings for both the original acquisition US and the reinstatement US to disentangle whether increased differential responding in the arousal measures after the reinstating USs reflects the return of old fear or rather the development of new fears and new danger expectancies linked to a different aversive outcome. Results showed that both the same-US and the different-US groups demonstrate the standard fear reinstatement effect in the skin conductance measure. Interestingly, however the different-US group showed elevated expectancy ratings for the US that had been presented during the reinstatement manipulation and not for the US that had been used to establish fear during acquisition. Hence, the authors coined the term "*cross-US reinstatement*" to describe this phenomenon and argued that clinical relapse attributed to reinstatement is not confined to the reactivation of old fears, but that it may embody new fears. Therefore, the *second aim* of the present study was to determine whether cross-US reinstatement can lead to the recovery of successfully extinguished conditioned fear of movement-related pain in healthy participants. That is, can an aversive but non-painful event (i.e. same valence, but qualitatively different) reinstate the fear that has been acquired with a painful US?

In sum, using the voluntary joystick movement paradigm, we investigated whether 1) fear of movement-related pain during the intention to perform a painful movement would be attenuated by reducing the contingency between motor intention and motor action, 2) a non-

painful but aversive US other than the acquisition US can be used to establish cross-US reinstatement. The experimental design comprised three groups: a same-US, different-US and no-US group. Because the main research question entails whether non-painful events can lead to the recovery of pain-related fear, all groups received acquisition with the painful US (i.e. electrocutaneous stimulus). The reinstatement US manipulation depended on group and consisted of an aversive, but non-painful stimulus in the different-US group (i.e. sound of a human scream). Based on the temporal proximity hypothesis and inhibition of delay, we hypothesized that 1) including inhibited movement trials in the design and as a consequence lowering the contingency between the motor intention and the motor action would lead to more successful inhibition of fear of movement-related pain during the mere intention to perform a painful movement (i.e. early CS component) and thus would not generate any differences between startle responses elicited during motor intention on CS+ and CS- trials. In addition, based on the findings of Sokol and Lovibond we hypothesized that at test 2) startle responses and verbal fear ratings would show reinstatement in both the same-US group and the different-US group, 3) US-expectancy ratings for the pain-US would be elevated in the same-US group, but that US-expectancy ratings for the sound-US would be elevated in the different-US group.

2. Methods

2.1. Participants

Sixty-six healthy participants (46 female; mean ± *SD* (range) age = 22 ± 4.47 (17-50) years) were compensated in two ways for their participation: 1) 4 psychology students of the University of Leuven received a course credit, and 2) 62 volunteers received €10. Participants were recruited by means of flyers distributed at the University of Leuven, advertisements (both online and on paper), and via the Experiment Management System (EMS) of the Faculty of Psychology and Educational Sciences of the University of Leuven

(Belgium) – this is an online application that allows psychology students, students in other disciplines, but also people from the general population to subscribe for experimental studies. Individuals who signed up for the study were invited to participate if they did not meet any of the following exclusion criteria: pregnancy, current or history of cardiovascular disease, chronic of acute respiratory disease (e.g., asthma, bronchitis), neurological disease (e.g., epilepsy), any current or past psychiatric disorder including clinical depression and panic/anxiety disorder, chronic pain, uncorrected hearing problems, painful wrist/hand or related problems, cardiac pacemaker or the presence of any other electronic, medical devices, and the presence of any other severe medical conditions. The experimental protocol was approved by the Ethical Committee of the Department of Psychology of the University of Leuven (registration number = S-55667). All 66 participants provided informed consent, which emphasized that they were allowed to terminate their participation at any time during the experiment.

2.2. Apparatus and experimental stimuli

2.2.1. Stimulus material

Two proprioceptive stimuli (i.e. moving a Logitech Attack 3 joystick to the left and to the right) served as CSs. The USs consisted of a painful electrocutaneous stimulus (pain-US) and a non-painful, yet aversive acoustic stimulus (sound-US). The *acoustic US* was a 2-s aversive human scream, presented in stereo at 100 dBA (Joos, Vansteenwegen, & Hermans, 2012; Meulders, Boddez, Vansteenwegen, & Baeyens, 2013; Van Diest, Bradley, Guerra, Van den Bergh, & Lang, 2009). The *pain-US* was an electrocutaneous stimulus (2 ms in duration) which was delivered by a commercial stimulator (DS7A; Digitimer, Welwyn Garden City, United Kingdom) through surface Sensormedics electrodes (8mm) filled with K–Y gel that were attached to the wrist of the dominant hand. During the calibration procedure, all participants received a series of electrocutaneous stimuli of increasing

intensity and were asked to rate each stimulus on a scale from 0 to 10, with '0' meaning "you feel nothing"; '1' indicating "you first feel something, but it is merely a stimulation"(detection threshold), '2' meaning, "this sensation starts to be painful, but it is still a mild pain" (pain threshold); up to '10' indicating "the worst pain imaginable". The individual pain-US intensity level selected during this calibration procedure, was tuned to yield a moderate pain, which demanded some effort to tolerate (participants were told that we aimed for a subjective stimulus intensity of 8 on this scale, but that this score was not binding). When the desired intensity level was reached, the experimenter assessed whether the participant agreed upon receiving repeated stimuli of this maximum intensity during the remainder of the experiment. The mean self-reported stimulus intensity was 8.29 (*SD* = 0.63, range = 6-9). The mean physical stimulus intensity was 33.79 mA (*SD* = 10.41, range = 14-64 mA). Note that during the calibration phase participants could notify the experimenter when they did not want to proceed receiving stimuli of a higher intensity at any time.

2.2.2. Software

The experiment was programmed using the free Windows-based experimental software package Affect 4.0 (Spruyt, Clarysse, Vansteenwegen, Baeyens, & Hermans, 2010), and was run on a Windows XP computer (Dell Optiplex 755) with 2 GB RAM and an Intel Core2 Duo processor at 2.33 GHz and an ATI Radeon 2400 graphics card with 256 MB of video RAM.

2.3.Procedure

The experiment was run during a 60-minute session. Participants were randomly allocated to one of three groups (same-US, different-US or no-US). The experimental trials were divided into four phases: acquisition, extinction, reinstatement, and test (see Table 1); these phases were run after four pre-experimental phases: preparation, practice and startle

probe habituation and sound-US familiarization. This general design was consistent with past human reinstatement studies (Hermans et al., 2005; LaBar & Phelps, 2005; Norrholm et al., 2006). During acquisition, a differential conditioning paradigm was adopted whereby participants were taught Pavlovian contingencies between one movement (CS+) and the pain-US and between another movement (CS-) and no pain-US. The direction of the joystick movement that served as the CS+ and CS- was counterbalanced across participants. For example, half of the participants received the pain-US after moving the joystick to the right; the other half received the pain-US when moving to the left. During extinction, the CS+ movement was no longer followed by the pain-US. Throughout both phases participants could freely choose the direction in which they were going to move on a given trial with the restriction that they had to move 4 times to the left and 4 times to the right in each block. The Reinstatement phase involved either 2 unsignaled pain-US presentations, 2 unsignaled sound-US presentations or no US presentations depending on the participant's experimental group. Some participants were exposed to the same US as that used in acquisition (same-US group) while others experienced a different US (different-US group), or no USs at all (no-US group). In the final test phase, the effects of the reinstating pain-USs on the return of fear of movement-related pain were tested. The test consisted of 4 CS+ and 4 CS- movements, none of these were reinforced by the pain-US.

2.3.1. Preparation phase

Upon arrival to the laboratory, participants were informed that the experiment involved the repeated presentation of electrocutaneous stimuli, short loud noises and the sound of a human scream. Participants were also told that they were free to decline participation at any time without any negative consequences. After providing informed consent, electrodes for eyeblink startle responses and the administration of the

electrocutaneous stimulus were attached and the calibration procedure of the pain-US was initiated (see Stimulus material section).

2.3.2. Practice phase

Prior to the practice phase, participants received extensive written instructions explaining the experimental Voluntary Joystick Movement (VJM) task. During each block participants performed 8 joystick movements (4 to the left/4 to the right) as quickly and as accurately as possible and had to inhibit their movements on 4 trials that they chose to move to the left and on 4 trials that they chose to move to the right. Before each movement participants were asked to verbally indicate whether they were going to move to the left or to the right. Subsequently, when a starting signal "+" appeared on the screen, they performed their movement of choice. However, when the starting signal was encircled "⊕" participants had to inhibit the movement and wait until a new trial began. Counter bars, divided in four equal segments, were positioned on the left and right sides of the computer screen. When a movement was successfully performed, one of the respective segments of the corresponding counter bar colored blue. By virtue of this online visual feedback, participants could immediately ascertain how many movements in each direction remained to be carried out (see Figure 1 for a detailed flow chart of the task). During the practice phase, two blocks of eight trials were run; no acoustic startle probes, pain-USs or sound-USs were presented.

2.3.3. Startle probe habituation

Because it is expected that the first responses to the startle probes are significantly larger than the latter ones, we inserted a startle probe habituation phase to correct for such possible confound in the data collection. This phase consisted of eight trials, each lasting 24 s. During each trial one startle probe was presented either between the 1st and the 2nd second (three trials), at the 10th second (two trials), or between the 15th and the 17th second (three

trials) after trial-onset. During this phase the participants wore headphones, and the lights in the experimental room were dimmed.

2.3.4. Sound-US familiarization

To familiarize the participants with the sound of the human scream that could be administered during the experiment (by analogy of familiarization to the electrocutaneous stimulus during the calibration phase and the noise probes during the startle habituation phase), we let them hear the human scream two times before the experiment started. Participants rated how painful and unpleasant they perceived this stimulus using two different Likert scales, one with anchors "not unpleasant at all" and "extremely unpleasant", and another with anchors "not painful at all" and "extremely painful". Both scales were accompanied by a different question, respectively 1) *How unpleasant did you find the human scream?* and, 2) *How painful did you find the human scream*. .

2.3.5. Acquisition phase

The acquisition phase was basically the same as the practice phase with the exception that: 1) pain-USs and startle probes were presented, 2) three instead of two blocks of eight trials were run; and 3) instructions now emphasized to pay close attention to the starting signal "+" and to respond as accurately and as fast as possible upon its appearance. One second after trial onset, the following sentence was projected on the screen "*Which movement are you going to perform during this trial – the left or the right movement?*". Participants then verbally reported in which direction they were going to move. Next, a variable intention delay (3-5 seconds) was inserted during which participants kept their choice in mind and prepared to perform the chosen movement (i.e., motor intention). During this intention delay the following sentence appeared on the computer screen: "*Keep your choice in mind and move as fast and accurate as possible when the "+" appears.*" After completing the CS movement, an

intertrial interval (ITI) of six seconds was inserted. Each CS+ trial was reinforced with the pain-US, immediately after completing the movement. When the encircled starting signal ⊕ appeared, participants were not allowed to move and thus never received reinforcement on these inhibited trials. CS- trials were also never reinforced by the pain-US. In each block with eight movements, 4 startle probes were given during the CS movement (2 during CS+ and 2 during CS-), 4 were presented during the intention delay (2 during CS- and CS+ trials) and another 4 during the ITI (2 during CS- and CS+ trials). On the inhibited trials (i.e., when participants inhibited performing the movement of their choice) startle probes could only be presented during the intention delay and the inter-trial interval. As a consequence, and inherent to the design, eyeblink startle responses during the CS movements could never be measured during inhibited trials. Participants were not informed about the contingencies between the joystick movements and the pain-USs. At the end of each conditioning block, participants had to rate their fear of movement-related pain for each of the CS movements on an 11-point Likert scale.

2.3.6. Extinction phase

The extinction phase was identical to the acquisition phase except that CS+ movements were no longer followed by the pain-US. For the delivery of the startle probes, the same time schedule was used as during acquisition.

2.3.7. Reinstatement and test of return of fear

During the reinstatement phase both same-US group and the different-US group received two unsignaled US-only presentations (i.e., USs that were not preceded by a CS movement), while control subjects in the no-US group received no US presentations during an equivalent time period. The background of the computer screen was plain black during the reinstatement phase for all experimental groups. The first reinstatement US was presented after a random

pause between 6-10 s, then a interstimulus interval of 3 s was inserted, followed by the second reinstatement US, and finally a pause of 2 s was inserted before the test block was initiated. Note that the different-US group received a novel sound-US (human scream), that was qualitatively different, but of the same valence as the original acquisition-US (electrocutaneous stimulus). In contrast, the same-US group received unsignaled presentations of the original acquisition-US during reinstatement. Next, we tested the effects of both the standard and the cross-US reinstatement procedure on return of fear under extinction by presenting one test block. These test trials were identical to the extinction trials.

2.4.Measurements

2.4.1. Self-reported fear of movement-related pain

After completing each conditioning block, participants reported how afraid they were to perform the right/left movement. Fear of movement-related pain in response to each of the CSs was rated on an 11-point Likert scale (range 0-10) with labels “not at all” to “very much”.

2.4.2. Fear-potentiated startle modulation

The startle reflex is a cross-species full-body reflex, triggered by startle-evoking stimuli (e.g. an acoustic startle probe), and modulated by defensive system activation. In particular, when anticipating threat, the startle reflex is potentiated as compared to no-threat control conditions, for instance in aversive conditioning paradigms or when participants are verbally instructed that they might receive a painful/aversive stimulus during sustained threat periods (Bublatzky, Guerra, Pastor, Schupp, & Vila, 2013; C. Grillon, 2008). In this study, electromyographic activity of the orbicularis oculi (the muscle that closes the eye during a blink), elicited by an acoustic startle probe, was recorded as an index of the eyeblink component of the startle response. Prior to the placement of each electrode, a skin peeling

cream was used to reduce inter-electrode resistance. Eyeblink activity was recorded from the orbicularis oculi muscle with 3 Ag/AgCl Sensormedics electrodes filled with electrolyte gel. The electrodes were placed on the skin surface overlaying the orbicularis oculi muscle, as recommended by Blumenthal et al. (Blumenthal et al., 2005). The raw signal was amplified by a Coulbourn isolated bioamplifier with bandpass filter (LabLinc v75–04). The recording bandwidth of the EMG signal was between 90 Hz and 1 kHz (±3 dB). The signal was rectified online and smoothed by a Coulbourn multifunction integrator (LabLinc v76–23 A) with a time constant of 20 ms. The EMG signal was digitized at 1000 Hz from 200 ms before the onset of the auditory startle probe until 1000 ms after probe onset. The startle probe was a 100 dBA burst of white noise with instantaneous rise time presented binaurally for 50 ms through headphones (Philips SHP2500). In the present study, eyeblink startle responses elicited by startle probes delivered during the CS movements served as an index for fear of movement-related pain or *cued pain-related fear*, whereas startle responses elicited by startle probes delivered during the intertrial interval (ITI) served as an index for *contextual pain-related fear.* During the intention delay interval, we also delivered startle probes, making it possible to examine *intentional cued pain-related fear* (i.e. stimulus-specific pain-related fear during motor intention).

2.4.3. Retrospective expectancy of the pain-US and the sound-US

After the test of reinstatement, participants were asked to report how much they expected the pain-US to occur when they performed the CS movements. A similar question assessed how much participants expected the occurrence of the sound-US when they performed the CS movements: "*How much did you expect the scream/electrocutaneous stimulus to occur when you moved to the left/right?"*. The order of these questions was randomized across participants.

2.5.Questionnaires

Shortly after participants completed the experiment, they filled out a battery of questionnaires to assess individual differences in psychological traits such as pain catastrophizing (Pain Catastrophizing Scale) (Sullivan, Bishop, & Pivik, 1995; Van Damme et al., 2000), trait anxiety (trait portion of the State-Trait Anxiety Inventory) (Spielberger, 1983; van der Ploeg, 2000), positive and negative affect (Positive and Negative Affect Schedule) (Engelen, De Peuter, Victoir, Van Diest, & Van Den Bergh, 2006; Watson, Clark, & Tellegen, 1988), and fear of pain (Fear of Pain Questionnaire)(McNeil & Rainwater, 1998; Roelofs, Peters, Deutz, Spijker, & Vlaeyen, 2005) that are known to affect the acquisition, extinction and return of pain-related fear. Therefore, we wanted to check for unintended differences in these traits between our experimental groups, in order to control for a possible group bias (see Table 2).

2.6. Experimental setting

Participants were seated in an office chair in a sound-attenuated experimental room, adjacent to the experimenter's room. After the practice phase, the lights in the experimental room were dimmed. An intercom system provided the possibility of verbal communication between the participant and the experimenter. Furthermore, the participant and her/his physiological responses could be monitored in the experimenter's room by means of a closed-circuit TV installation and computer monitors.

2.7. Data analysis overview

Using PsychoPHysiological Analysis (PSPHA)(de Clercq, Verschuere, de Vlieger, & Crombez, 2006), a modular script-based program, we calculated the peak amplitudes defined as the maximum of the response curve within 21 – 300 ms after the startle probe onset. All startle waveforms were visually inspected off-line, and technical abnormalities and artifacts

were eliminated using the PSPHA software. Every peak amplitude was calculated by subtracting its baseline score (averaged EMG level between 1 and 20 ms after the probe onset). The raw scores were transformed to *z*-scores to account for inter-individual differences in physiological reactivity. In order to optimize the visualization of the startle data and avoid negative values on the Y-axis, T-scores –a linear transformation of the z-scores– were used in the figures. Averages were calculated per block for responses during the variable intention delay (motor intention), the CS movements (motor action), and the ITI (context alone).

Separate repeated measures (RM) ANOVAs were run to examine the acquisition, extinction, and reinstatement effects in the diverse dependent measures. Because the procedure was exactly the same during the acquisition and extinction phases for both experimental groups, no interactions with the Group variable was anticipated at this point. Acquisition effects in the *self-reported fear of movement-related pain* were analyzed using a RM ANOVA with Group as between-subjects factor (3 levels – Same-US/Different-US/No-US) and with Stimulus Type (2 levels – CS+/CS-) and Block (3 levels – a1-3) as within-subjects factors. Extinction effects were evaluated using a RM ANOVA with Group as between-subjects factor (3 levels – Same-US/Different-US/No-US) and with Stimulus Type (2 levels – CS+/CS-) and Block (2 levels – a3/e3) as within-subjects factors. Return of fear was tested with a RM ANOVA with Group as between-subjects factor (3 levels – Same-US/Different-US/No-US) and with Stimulus Type (2 levels – CS+/CS-) and Block (2 levels – e3/test) as within-subjects factors.

The *startle eyeblink responses* were analyzed in two similar separate sets of analyses to evaluate motor intention effects and motor action effects, respectively comparing motor intention and ITI startle responses and motor action and ITI startle responses. In particular, Acquisition of fear of movement-related pain during *motor intention* was analyzed using a RM ANOVA with Group as between-subjects factor (3 levels – Same-US/Different-US/No-

US) and with Stimulus Type (2 levels – CS+/CS-), Timing (2 levels – ITI/intention), and Block (3 levels – a1/a2/a3) as within-subjects factors. Because there was no reliable acquisition effect, extinction and reinstatement effects were not further analyzed and reported. Acquisition and extinction of psychophysiological fear responding to the *movement itself* was analyzed using a RM ANOVA with Group as between-subjects factor (3 levels – Same-US/Different-US/No-US) and with Stimulus Type (2 levels – CS+/CS-), Timing (2 levels – ITI/movement), and Phase (2 levels – acquisition/extinction) as within-subjects factors on the mean startle amplitudes averaged over phase[1]. Return of psychophysiological fear responding was tested with a RM ANOVA with Group as between-subjects factor (3 levels – Same-US/Different-US/No-US) and with Stimulus Type (2 levels – CS+/CS-), Timing (2 levels – ITI/movement), and Phase (2 levels – e3/test) as within-subjects factors. Greenhouse-Geisser corrections are reported when appropriate. Uncorrected degrees of freedom and corrected p-values are reported together with ε and the effect size indication η_p^2 for significant effects. Because we had clear a priori hypotheses, data were further analyzed using planned comparisons.

3. Results

3.1. US characteristics and questionnaires

The experimental groups did not have significantly different scores on any of the psychological trait questionnaires (see Table 2). We ran simple ANOVAs with Group as between-subjects factor (3 levels – Same-US/ Different-US/No-US) to evaluate possible group differences in electrocutaneous stimulus intensity (physically and self-reported) chosen during the calibration phase. There were no differences among the three groups (main effect

[1] This approach was chosen for sake of simplicity, because no interaction with Group was anticipated or occurred at this point, and no interactions with Block emerged within each phase, except for the main effect of Block indicating overall startle probe habituation.

Group: $F(2,63) = 1.51$, $p = .23$, $\eta_p^2 = .04$). Mean (±SD) physical pain-US intensity (in mA) was 32.09 (±10.23) in the same-US group, 32.36 (±7.50) in the no-US group, and 36.91 (±12.65) in the different-US group. The self-reported intensity of the pain-US also did not differ between groups (Group: $F(2,63) = 1.45$, $p = .24$, $\eta_p^2 = .04$). Mean (±SD) self-reported pain intensity was 8.27 (±0.55) in the same-US group, 8.45 (±0.51) in the no-US group, and 8.14 (±0.77) in the different-US group.

We conducted a RM ANOVA with as between-subjects factor Group (3 levels – Same-US/ Different-US/No-US) and as within-subjects factor Rating (2 levels – unpleasantness/painfulness) on the sound-US familiarization ratings. There were no differences between the experimental groups in how painful and unpleasant they rated the human scream before the experiment started (main effect Group: $F < 1$). Participants in all groups rated the human scream as being more unpleasant than painful (main effect Rating: $F(1,63) = 61.35$, $p < .001$, $\eta_p^2 = .49$). Mean (±SD) unpleasantness score for the human scream was 5.86 (±1.81) in the same-US group, 6.09 (±2.62) in the no-US group, and 5.91 (±1.66) in the different-US group. Mean (±SD) painfulness score for the human scream was 4.45 (±2.48) in the same-US group, 4.86 (±2.96) in the no-US group, and 3.55 (±1.90) in the different-US group. As expected, the Group x Rating interaction, ($F(1,63) = 2.74$, $p = .07$) was not significant.

3.2. Fear-potentiated startle modulation

3.2.1. Motor intention vs. context alone

<u>Acquisition fear of movement-related pain</u>

Figure 2 shows the mean startle eyeblink amplitudes elicited during the motor intention and during the context alone on CS+ and CS- trials respectively. Overall, startle

responses elicited by probes during the intention delay were higher as compared to those presented during the context alone (main effect of Timing: $F(1,63) = 21.07$, $p < .0001$, $\eta_p^2 = .25$), and this difference was larger for the CS+ trials than for the CS- trials (Stimulus Type x Timing interaction: $F(1,63) = 5.62$, $p < .05$, $\eta_p^2 = .08$). This difference did not change across blocks, (Stimulus Type x Timing x Block interaction: $F < 1$), and was not modulated by Group (Stimulus Type x Timing x Group, $F(2,63) = 1.54$, $p = .22$). Planned comparisons, however, could not confirm the difference between startle amplitudes during the intention delay of the CS+ trial and the CS- trial, ($F(1,63) = 3.36$, $p = .07$), as this difference just failed to reach significance. There was no difference in startle responding during the context alone for both trial types, ($F(1,63) = 2.32$, $p = .13$).

Extinction and return of fear of movement-related pain

Because there was no reliable differential acquisition of fear of movement-related pain during motor intention, extinction and reinstatement effects will not be reported in detail in order not to overload the results section.

3.2.2. Motor action vs. context alone

Acquisition and extinction of fear of movement-related pain

Figure 3 shows the average eyeblink startle amplitudes during the acquisition and the extinction phase elicited during the movement and the context alone on the CS+ and the CS- trials separately. Overall, average startle responses during the movements were higher than those during the context alone (main effect of Timing: $F(1,63) = 64.30$, $p < .0001$, $\eta_p^2 = .51$), and this difference was larger for the CS+ trials than for the CS- trials (Stimulus Type x Timing interaction: $F(1,63) = 12.05$, $p < .0001$, $\eta_p^2 = .16$). Also, this difference changed across phases, (Stimulus Type x Timing x Phase interaction: $F(1,63) = 9.10$, $p < .0001$, $\eta_p^2 = .13$),

despite a general decrease in startle responses over phases (main effect of Phase: $F(1,63) = 86.31$, $p < .0001$, $\eta_p^2 = .58$). These effects were also modulated by Group (Stimulus Type x Timing x Phase x Group, $F(2,63) = 3.31$, $p < .05$, $\eta_p^2 = .10$). As expected, planned comparisons further confirmed that average startle amplitudes in the acquisition phase during the CS+ movement were higher than during the CS- movement, ($F(1,63) = 12.27$, $p = .001$), but there was no significant difference between the startle amplitudes on both trial types during the context alone, ($F(1,63) = 3.01$, $p = .09$). Furthermore and in line with our expectations, the difference between startle responses elicited by the CS+ and the CS- movements disappeared during the extinction phase in both groups (both Fs < 1). These data show differential pain-related fear acquisition to the painful movement but not to the context alone, and subsequent successful extinction of the previously acquired fear of movement-related pain.

Return of fear of movement-related pain

Figure 4 shows the mean startle amplitudes at the end of extinction (e3) and during test for the CS+ and the CS- movements and for all experimental groups separately. There was a significant main effect of Timing, $F(1, 63) = 25.71$, $p < .0001$, $\eta_p^2 = .29$, indicating that startle responses elicited during the movements were higher than those elicited during the context alone. Furthermore, there was a significant Phase x Group interaction, $F(1, 63) = 7.68$, $p < .01$, $\eta_p^2 = .20$, suggesting that there were differences in startle responding at the end of extinction compared with the test depending on Group. Even though the Stimulus Type x Phase x Group interaction was not significant ($F < 1$), we continued to test our a priori hypotheses. In contrast with our hypothesis, there was no significant Stimulus Type x Phase interaction in the same-US group, ($F(1,63) = 1.44$, $p = .23$). However, after being exposed to two unsignaled pain-USs, participants in the same-US group show increased pain-US expectancy ratings for both the CS+ movement and the CS- movement, ($F(1,63) = 8.17$, $p <$

.01) suggesting that there was a non-differential reinstatement effect. Second, there was no significant Stimulus Type x Phase interaction for the no-US group (F<1). In line with our expectations, the participants in the control group who were not exposed to any USs during the reinstatement procedure showed no increases to any of the CS movements (F<1). In the different-US group also no differential nor non-differential return of fear was observed (F < 1). These data suggest that there is a non-differential return of fear to both movements, only in the same-US group, but not in the different-US or control group.

3.3. Self-reported fear of movement-related pain

Acquisition fear of movement-related pain

Figure 5 shows the mean self-reported fear provoked by each of the joystick movements. As expected, fear ratings were higher for the (CS+) movement that was consistently followed by the pain-US than for the (CS-) movement that was never followed by the pain-US (main effect Stimulus Type: $F(1, 63) = 147.10$, $p < .0001$, $\eta_p^2 = .70$). Of crucial importance, this differential conditioned fear responding gradually built up over time (Stimulus Type x Block interaction: $F(2, 126) = 4.31$, $p < .05$, $\varepsilon = .72$, $\eta_p^2 = .06$) and as expected this fear learning interaction was not modulated by Group (Stimulus Type x Block x Group interaction: F<1). These results indicate that differential pain-related fear was acquired in all experimental groups.

Extinction of fear of movement-related pain

Self-reported fear elicited by the CS+ movement was overall still higher than for the CS- movement (main effect Stimulus Type: $F(1, 63) = 121.25$, $p < .0001$, $\eta_p^2 = .66$), but fear reports generally decreased from the end of acquisition to the end of extinction (main effect Block: $F(1, 63) = 170.24$, $p < .0001$, $\eta_p^2 = .53$). More importantly, the differences in

conditioned fear elicited by the CS+ and the CS- movements gradually declined during the extinction phase (Stimulus Type x Block interaction: $F(1, 63) = 98.63$, $p < .0001$, $\eta_p^2 = .61$, as expected this interaction was not modulated by Group, (Stimulus Type x Block x Group interaction: $F < 1$). These data indicate that there was successful reduction of pain-related fear in all experimental groups.

Return of fear of movement-related pain

The data pattern shown in Figure 5 suggests that fear of movement-related pain reappeared in the same-US group at test, but not in the no-US group nor in different-US group. In general, conditioned fear responses were higher at test than at the end of the extinction phase (main effect Block: $F(1, 63) = 14.81$, $p < .001$, $\eta_p^2 = .19$) and they were higher for the CS+ movement than for the CS- movement (main effect Stimulus Type: $F(1, 63) = 15.77$, $p < .001$, $\eta_p^2 = .20$). A significant Block x Group interaction emerged, ($F(2, 63) = 5.83$, $p < .01$, $\eta_p^2 = .16$), suggesting that conditioned fear responding was higher during the test of reinstatement compared with the end of extinction in the same-US group, but not in the no-US group or the different-US group, but this 2-way interaction did not accommodate the anticipated 3-way interaction, (Stimulus Type x Block x Group interaction: $F(2, 63) = 2.55$, $p = .09$, $\eta_p^2 = .07$). Although the 3-way interaction did not reach significance, we further tested our a priori hypotheses. Planned within-group comparisons confirmed that the increase (e3 *vs.* test) in conditioned fear of the CS+ movement was larger than of the CS- movement in the same-US group, ($F(1, 63) = 5.81$, $p < .05$), but not in the different-US group, ($F<1$) or in the no-US group, ($F(1, 63) = 1.68$, $p = .20$). Although, this is indicative of a differential reinstatement effect, planned comparisons further revealed that participants in the same-US group reported increased fear in response to the CS+ movement, ($F(1,63) = 31.00$, $p < .0001$), as well as to the CS- movement, ($F(1,63) = 11.81$, $p < .01$), but to a lesser extent.

3.4. Expectancy of the pain-US and the sound-US after reinstatement

Figure 6 shows the expectancy ratings for the pain-US and the sound-US after the reinstatement procedure for all experimental groups separately. Even though the Stimulus Type x US Type x Group interaction was not significant (F<1), we continued to test our a priori hypotheses. Interestingly, groups differed in their expectancy ratings for both types of USs (US Type x Group interaction, $F(1, 63) = 4.56$, $p < .05$). First, there was a significant Stimulus Type x US Type interaction in the same-US group ($F(1, 63) = 6.59$, $p < .05$). As expected, after being exposed to two unsignaled pain-USs, participants in the same-US group show increased pain-US expectancy ratings for the CS+ movement as compared to the CS- movement, ($F(1, 63) = 15.10$, $p < .001$), but no differences in sound-US expectancies, (F<1). Second, there was also a significant Stimulus Type x US Type interaction for the no-US group ($F(1, 63) = 8.19$, $p < .01$). Contrary to our expectations, the participants in the control group who were not exposed to any USs during the reinstatement procedure also showed higher expectancies for the pain-US in response to CS+ movement than to the CS- movement, ($F(1,63) = 12.30$, $p < .001$), again no such differences were found for the sound-US expectancies ($F < 1$). Third, no significant Stimulus Type x US Type interaction emerged in the different-US group ($F(1,63) = 2.85$, p =.10). Contrary to our expectations, after being exposed to two unsignaled sound-USs, participants in the different-US group show increased pain-US expectancies for the CS+ movement compared with the CS- movement, ($F(1,63) = 10.38$, $p < .01$), but no differences in expectancies for the sound-US, ($F(1,63) = 1.87$, $p = .18$). In line with our expectations however, sound-US expectancies in this group were indeed higher than in the same-US group, ($F(1,63) = 8.47$, $p < .01$), as well as in the no-US group, ($F(1,63) = 4.64$, $p < .05$), but expectancies did not differ for the CS+ and the CS- movements.

4. Discussion

The first goal of this study was to determine whether fear of movement-related pain during the intention to perform a painful movement would be inhibited in healthy participants when the contingency between the motor intention and motor action was reduced. The second goal of this study was to address the pertinent clinical question of whether a non-painful, stressful or aversive event can lead to the return of successfully extinguished fear of movement-related pain. So far, experimental research on the return of pain-related fear in the context of pain is limited. But there are several real-life examples of return of pain-related fear and avoidance behavior after a non-painful but stressful life event. For example, fear of pain might return after stigmatizing remarks of colleagues when patients return to work, after a family/marital conflict, or after financial problems (often related to insurance or disability allowances) and the accompanying feelings of injustice.

With respect to the first research question, we found that in contrast with the findings of Meulders and Vlaeyen (Meulders & Vlaeyen, 2013b), the startle probes during the intention delay did not generate higher responses during CS+ trials than CS- trials. As expected, we showed that when we eliminated the artificial perfect simultaneity between motor intention and motor action, the fear of movement-related pain triggered during motor intention was attenuated and the differences in startle responding during the CS+ versus CS- trials during motor intention and context alone were no longer significant.

In line with predictions and previous empirical findings (Hermans et al., 2005; LaBar & Phelps, 2005), the same-US group showed more increase in verbal fear ratings for CS+ than the CS- at test compared with the end of extinction. This data pattern reflects the standard differential reinstatement effect. As expected, this effect was not observed in the no-US group. The results of the startle measures corroborated these findings in the same-US group, however the elevated startle activation at test was not confined to the CS+ movement but was also present for the CS-. This data pattern thus rather reflects a non-differential reinstatement

effect that again was not manifest in the no-US group. Finally, in our US-expectancy measures during test, we found pain-US expectancy ratings to be elevated for the CS+ movement but not the CS- movement, but this differential reinstatement effect was not observed in the sound-US expectancy ratings in the same-US group. Contrary to our expectations, in the no-US group a similar differential increase in pain-US expectancy was present possibly indicating spontaneous recovery effects. In line with this explanation, no such increase was found for the sound-US expectancy.

The results of the same-US group involves an essential replication of previous research findings, however, the main focus of this study was the different-US group in which cross-US reinstatement was under investigation. In contrast with our expectations and the previous findings reported by Sokol and Lovibond (Sokol & Lovibond, 2012), the startle responses nor the verbal pain-related fear ratings were elevated at test in the different-US group. Basically, the data pattern mimicked the one observed in the no-US group instead of the one observed in the same-US group. Interestingly, in the US-expectancy ratings a different pattern emerged. As expected and in line with the findings of Sokol and Lovibond, the different-US group showed increased sound-US expectancy at test compared with the no-US and the same-US groups. Unexpectedly, however pain-US expectancy ratings were also elevated selectively for the CS+ movement, after the presentation of two unsignaled sound-US presentations. These results show a discrepancy between the startle responses and the verbal ratings on the one hand, and the US-expectancy ratings on the other hand: in the former the anticipated cross-US reinstatement effect was absent, whereas in the latter the increased sound-US expectancy provides evidence for cross-US reinstatement.

Some of these findings deserve a more in-depth discussion. *First*, we observed both non-differential and differential reinstatement effects in the same-US group. The verbal pain-related fear and the pain-US expectancy ratings both showed an increase from the end of

extinction to test, and this increase was more pronounced for the CS+ movement than for the CS- movement (differential), whereas in the startle responses both movements elicited increased fear-potentiated activation (non-differential). Previously, both differential (Dirikx et al., 2007; Hermans et al., 2005; Norrholm et al., 2006) and non-differential (Dirikx et al., 2004; Dirikx et al., 2009; Milad et al., 2005; Sokol & Lovibond, 2012) reinstatement effects whereby fear in response to both the CS+ and the CS- increases after re-exposure to the US, have been reported in humans. The observation that a CS- which was never paired with the US can induce increased eyeblink startle responses at test suggests that previously safe stimuli can become to elicit fear following a reinstatement experience. This is in line with the argument that in some cases, reinstatement manipulations may foster new fears. The allegedly underlying mechanism in most non-differential reinstatement explanations is *context conditioning* (Bouton, 2002; Bouton & Bolles, 1979; Dirikx et al., 2009; Westbrook, Iordanova, McNally, Richardson, & Harris, 2002). Unpredictability is known to induce context conditioning in both humans (Christian Grillon, 2002; Meulders, Vansteenwegen, & Vlaeyen, 2010; Vansteenwegen, Iberico, Vervliet, Marescau, & Hermans, 2008) and non-human animals (Fanselow, DeCola, & Young, 1993), that is, due to the absence of discrete predictors for the US, a context-US association will be formed. Likewise, after extinction, the presentation of the US is unexpected, therefore new contextual fears might be acquired as the result of the unpredictable US presentations in the absence of the CS presentations.

Second, the observed data pattern in the US expectancy ratings in the different-US group might be explained in a similar way. After the presentation of two unsignaled sound-USs, expectancy ratings for that US increased for both movements. It seems that the experimental situation as a whole had become more uncertain for these participants as they report to be expecting the sound-US at any time now. Remarkably, the pain-US expectancy ratings are increased as well, being exposed to the aversive and stressful human scream (sound-US) also

reinstated the differential pain-US expectancy for the original CS+ and CS- movements. This data pattern is suggestive of a summation mechanism whereby contextual fear combines with residual fear to the CS (Bouton, 1984; Bouton & Bolles, 1979). Moreover, the odds to develop contextual fear are raised when the reinstatement procedure is experienced as a context switch; that way the inhibition of the extinction context will concurrently be released. Probably, our participants experienced a change of context not only in the reinstatement groups (the US being unexpectedly presented again) but also in the no-US group (due to a short break during which the other groups received reinstating USs), which led to spontaneous recovery of the extinguished CS-US association.

Third, in contrast with the findings of Sokol and Lovibond, there is an obvious discrepancy between the US-expectancy ratings and verbal pain-related fear ratings and startle responses in the different-US group. It seems that the increase in pain-US and sound-US expectancy, paradoxically did not lead to increased pain-related fear ratings and startle responses. It is possible that, the context became more generally uncertain for the participants after the reinstatement experience, but because the US used during acquisition was qualitatively different (painful vs. unpleasant) and more intense accordingly leading to higher fear responses (Morris & Bouton, 2006), the threshold for pain-related fear reports and increased startle responding may not have been reached. These results suggest that a reinstatement US that is too different from the original acquisition US (qualitative difference) or a US that is less intense/salient (quantitative difference) than the acquisition US might not suffice to produce reinstatement effects.

Fourth, in the present study, we could not replicate the effect that mere intention to perform a painful movement can trigger pain-related fear in healthy participants. We adjusted the design to fit the daily life situation better, that is, intention for action is not necessarily followed by the intended behavior. For example the intention to quit smoking does not

necessarily lead to successful cessation of smoking. In our previous study (Meulders & Vlaeyen, 2013b), both motor intention and motor action were perfectly correlated, because participants always had to perform their movement of choice. In this follow-up experiment, two types of trials were included, movement trials, where the motor intention was indeed followed by the intended action and inhibited trials, where the action did not follow the motor intention. This more ecologically valid set-up not only matched better with theories of common human behavior, but also generated a more adaptive pattern of responding in healthy participants. In line with this reasoning, we would predict that chronic pain patients might not be able to inhibit the fear responses when they are merely thinking about a painful movement. By analogy of clinical anxiety, impaired inhibitory learning and a lack of inhibition of delay might in fact constitute vulnerability factors for the unbridled spreading of pain-related fear. Furthermore, previous research showed that just thinking about painful movements might even induce pain and swelling in the affected hand in chronic regional pain syndrome (CRPS) patients (Moseley, 2004; Moseley et al., 2008). It seems feasible, that in these earlier findings pain-related fear mediated the conditioned painful symptoms (for a similar argument see (Meulders & Vlaeyen, 2013b)). This idea is not outrageous since other physical health complaints have been susceptible to conditioning processes as well, for example health complaints such as lightheadedness, chest tightness, pounding heart and breathlessness have been conditioned in response to odors (CSs) and 20% CO_2-enriched air as the US (Fannes et al., 2008; Meulders, Fannes, et al., 2010; Van den Bergh et al., 2001; van den Bergh, Kempynck, van de Woestijne, Baeyens, & Eelen, 1995; Van den Bergh et al., 1999; Van den Bergh, Winters, Devriese, & Van Diest, 2002; Van Diest et al., 2006). Follow-up research should focus on patient populations or subclinical samples demonstrating a vulnerability to develop chronic pain problems (e.g. people with high scores on the pain catastrophizing scale,

fear of pain questionnaire, etc.) to determine whether they indeed show a failure to inhibit fear during motor intention as compared to healthy controls.

A couple of limitations should be outlined. *First*, although all participants received both USs before the conditioning procedure to get familiar with both stimuli, the sound-US was only presented again at the very end of the experiment in the different-US group only. Moreover, during acquisition and extinction, participants rated the US-expectancy for the US that was actually presented only, in order not to confuse participants. This might have influenced the US-expectancy ratings, because suddenly after the reinstating USs, new US-expectancy questions were added. *Second*, no *explicit control* for motor intention was included; hence we cannot undeniably confirm that participants actively captured their intention during the intention delay. Follow-up studies might include event-related potentials (ERP) as a manipulation check and to further disentangle the involvement of motor intention *vs*. motor preparation (Toni, Thoenissen, & Zilles, 2001). *Third*, although we followed the suggestion of Sokol and Lovibond to use the human scream as a US, we cannot disentangle at this point whether either the qualitative differences or the quantitative differences with the acquisition US (painful electrocutaneous stimulus) are responsible for the absence of the cross-US reinstatement effect in the fear of pain ratings and startle response. It can either be due to the fact that the human scream is not a painful stimulus, but it might also just be less intense on the unpleasantness scale. Future research using different reinstatement USs, including painful USs and other non-painful aversive USs might contribute significantly to our understanding of the minimal conditions to produce cross-US reinstatement of pain-related fear. *Fourth* and closely related, since we were interested whether a non-painful, stressful or aversive event could lead to the return of successfully extinguished fear of movement-related pain, we only used the pain-US as an acquisition US. Therefore, an alternative explanation might be that the sound-US is not an effective US in our paradigm.

To conclude, we demonstrated that reducing the perfect contingency between motor intention and motor action, led to successful inhibition of fear responses elicited by merely thinking about a painful movement. Further, we replicated the standard reinstatement effect, that is, a differential return of fear in the verbal ratings and the US-expectancy ratings, but a non-differential return of fear in the psychophysiological fear response. More importantly, we observed a differential cross-US reinstatement effect in the pain-US expectancy ratings and an non-differential increase in the sound-US expectancy ratings, only in the group that was exposed to another US than the one that was used to establish fear acquisition. However, this effect failed to materialize in the verbal fear ratings and the startle responses. Taken together, we only found partial support for the hypothesis that reinstatement experiences might foster the acquisition of new fears rather than reinstating old fears. Notwithstanding the fact that artificial laboratory studies always have to deal with a range of restrictions, they encompass important stepping-stones that pave the way for more naturalistic and applied clinical research. Future research should further address whether stressful, aversive but non-pain-related events can also reinstate fear of movement/re-injury or whether the exposure to these new stressors and aversive events simply generate new fears.

5. Conflict of interest statement

The authors report no conflict of interest.

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8. Figure captions

Figure 1. Flow chart of the experimental task for both an exemplary A. movement trial and B. inhibited trial . Note – the CS+ movement was only followed by the pain-US during acquisition, but not during extinction and the test of reinstatement. The pictograph surrounded by question marks serves as a signal to prompt the choice of movement direction; the drawing of a lightning bolt represents the presentation of the pain-US; the + represents the starting signal and the ⊕ represents the inhibition signal; the white arrow represents that CS movement direction on a certain trial. Coloring a segment of the counter bar (blue) represents successful movement execution.

Figure 2. Mean startle amplitudes (±SE) during the motor intention and the context alone (ITI) during the CS+ and the CS- trials for all experimental groups together (*N*= 66).

Figure 3. Mean startle amplitudes (±SE) during the motor action and the context alone (ITI) for both CS+ and the CS- trials during acquisition and extinction for all experimental groups together (*N*= 66).

Figure 4. Mean startle amplitudes (±SE) during the movement for both CS+ and the CS- trials at the end of extinction (e3) and the test of reinstatement (test) for the same-US group (*n* =22), the different-US group (*n* =22), and the no-US group (*n* =22) separately. Note that the lightning bolt represents the presentation of the electrocutaneous stimulus (pain-US) and the screaming face represents the presentation of the human scream (sound-US).

Figure 5. Mean self-reported fear of movement-related pain (±SE) for the same-US group (*n* =22), the different-US group (*n* =22), and the no-US group (*n* =22) separately during acquisition (a1-3), extinction (e1-3), and test of reinstatement (test). Note that the lightning bolt represents the presentation of the electrocutaneous stimulus (pain-US) and the screaming face represents the presentation of the human scream (sound-US).

Figure 6. Mean self-reported US-expectancy (±SE) for the pain-US and the sound-US on both CS+ and CS- trials for the same-US group (*n* =22), the different-US group (*n* =22), and the no-US group (*n* =22) separately. Note that the lightning bolt represents the electrocutaneous stimulus (pain-US) and the screaming face represents the human scream (sound-US).

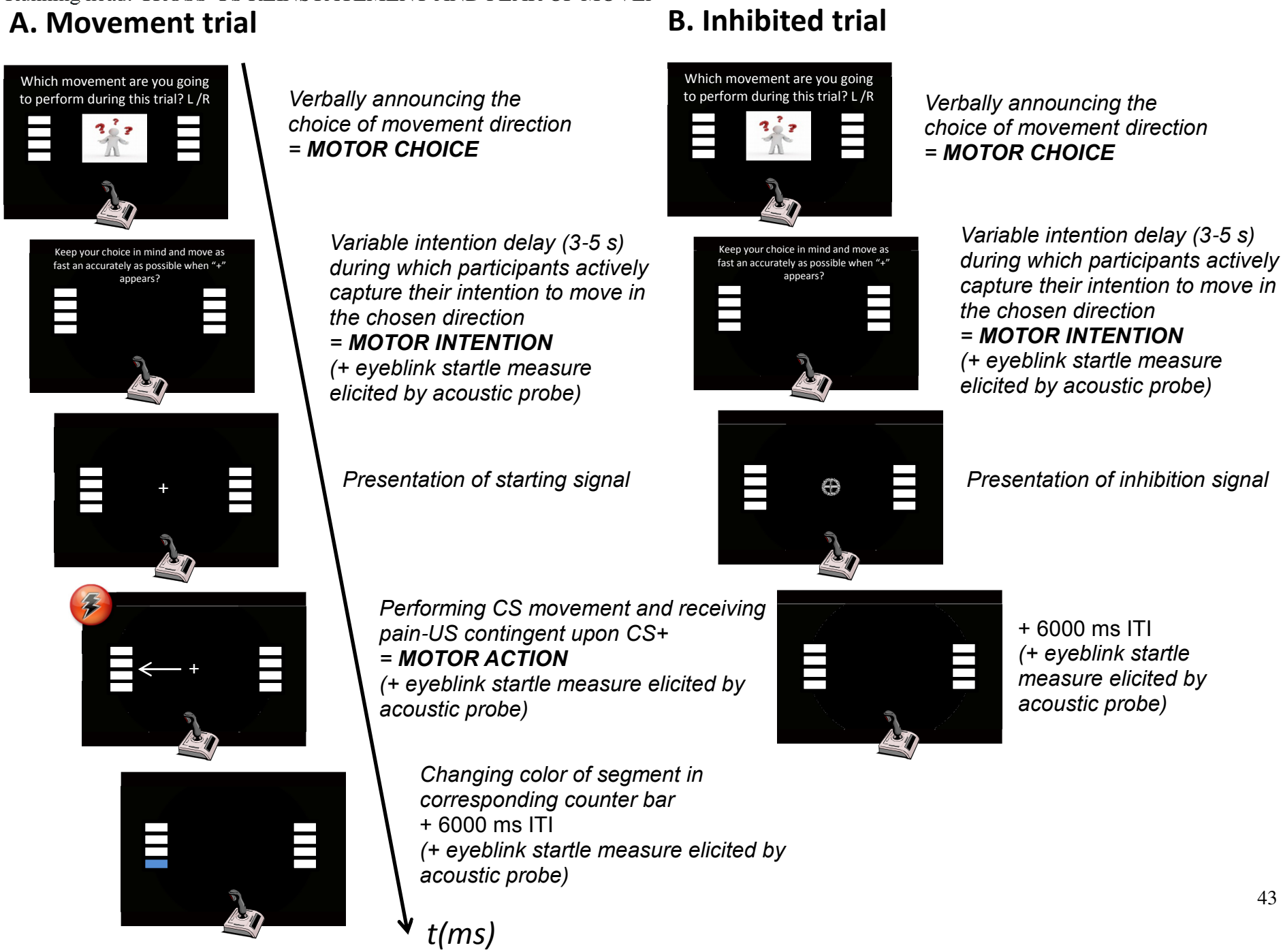
A. Movement trial
B. Inhibited trial
Which movement are you going to perform during this trial? L /R
Verbally announcing the choice of movement direction = MOTOR CHOICE
Keep your choice in mind and move as fast an accurately as possible when "+" appears?
Variable intention delay (3-5 s) during which participants actively capture their intention to move in the chosen direction = MOTOR INTENTION (+ eyeblink startle measure elicited by acoustic probe)
+
Presentation of starting signal
Presentation of inhibition signal
Performing CS movement and receiving pain-US contingent upon CS+ = MOTOR ACTION (+ eyeblink startle measure elicited by acoustic probe)
+ 6000 ms ITI (+ eyeblink startle measure elicited by acoustic probe)
Changing color of segment in corresponding counter bar
+ 6000 ms ITI
(+ eyeblink startle measure elicited by acoustic probe)
t(ms)

Figure 2.

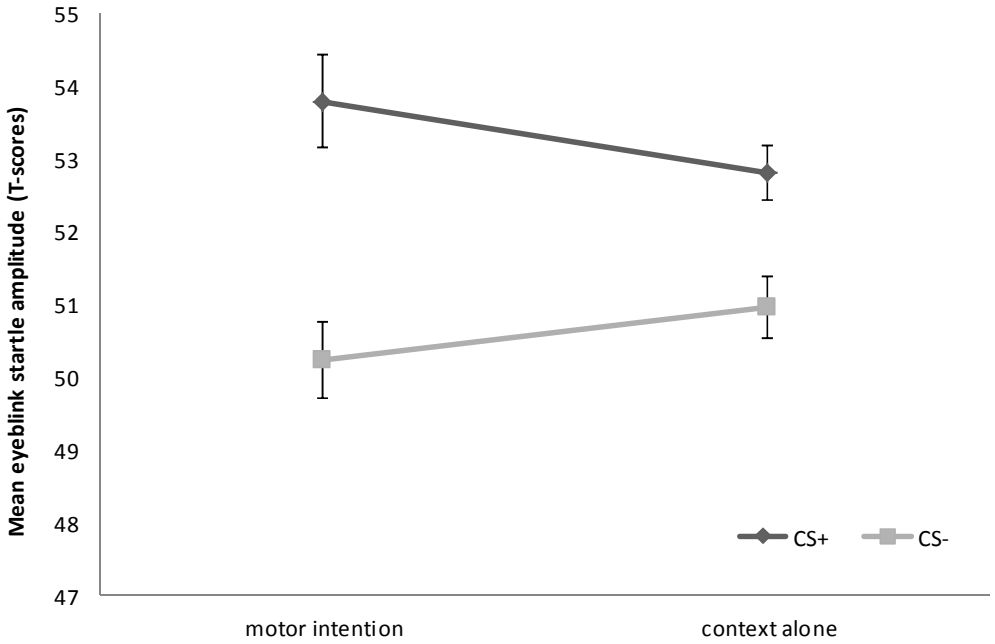
55
54
53
52
51
50
49
48
47
Mean eyeblink startle amplitude (T-scores)
CS+
CS-
motor intention
context alone

Figure 3.

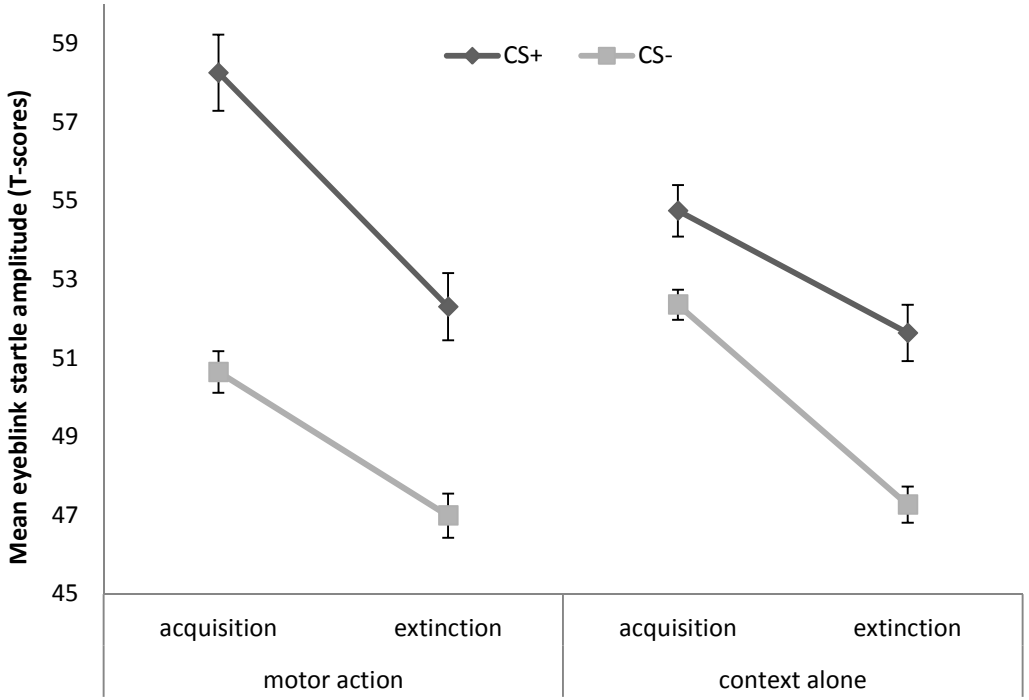
Mean eyeblink startle amplitude (T-scores)
59
57
55
53
51
49
47
45
CS+
CS-
acquisition
extinction
acquisition
extinction
motor action
context alone

Figure 4.

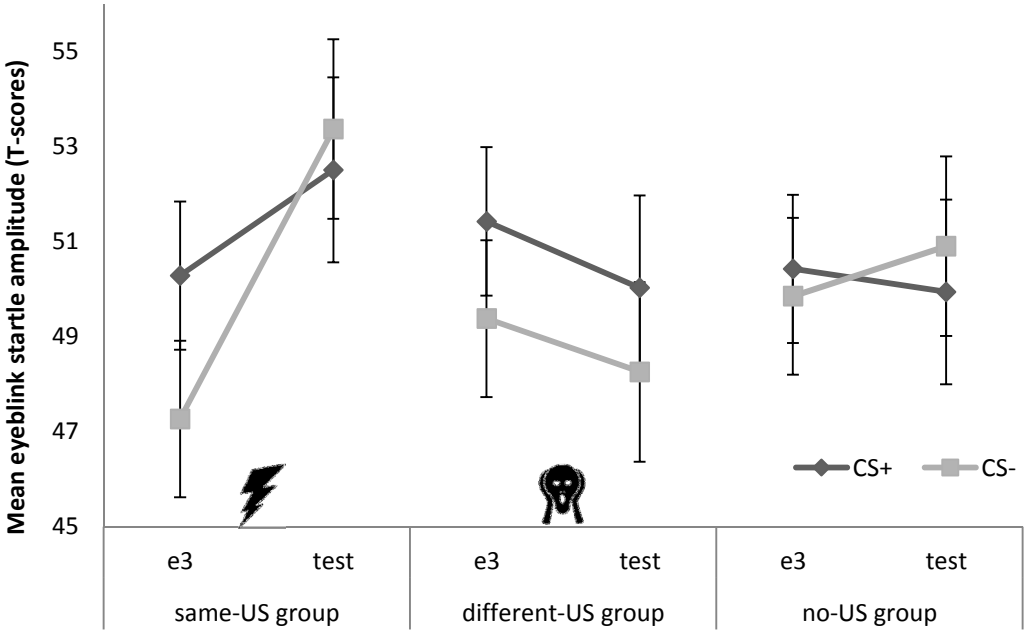
Mean eyeblink startle amplitude (T-scores)
55
53
51
49
47
45
CS+
CS-
e3
test
e3
test
e3
test
same-US group
different-US group
no-US group

Figure 5.

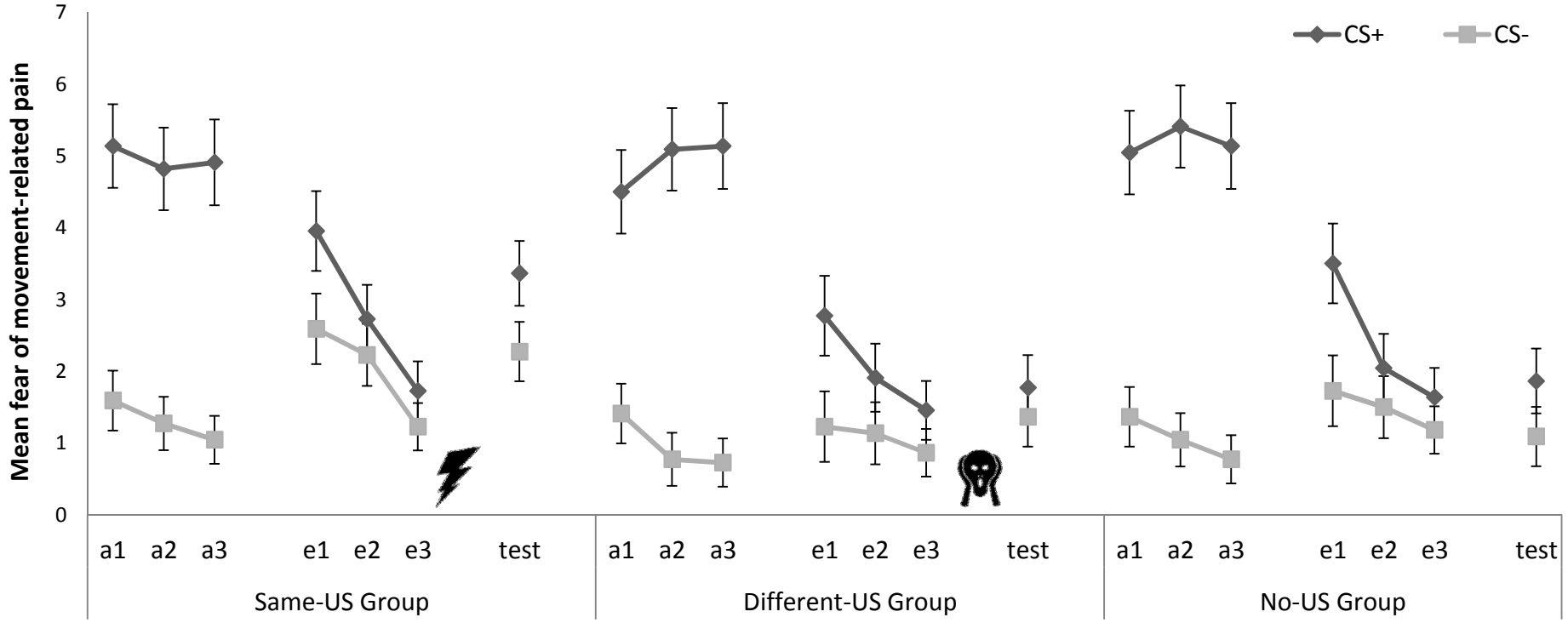
Mean fear of movement-related pain
0
1
2
3
4
5
6
7
CS+
CS-
a1
a2
a3
e1
e2
e3
test
Same-US Group
Different-US Group
No-US Group

Figure 6.

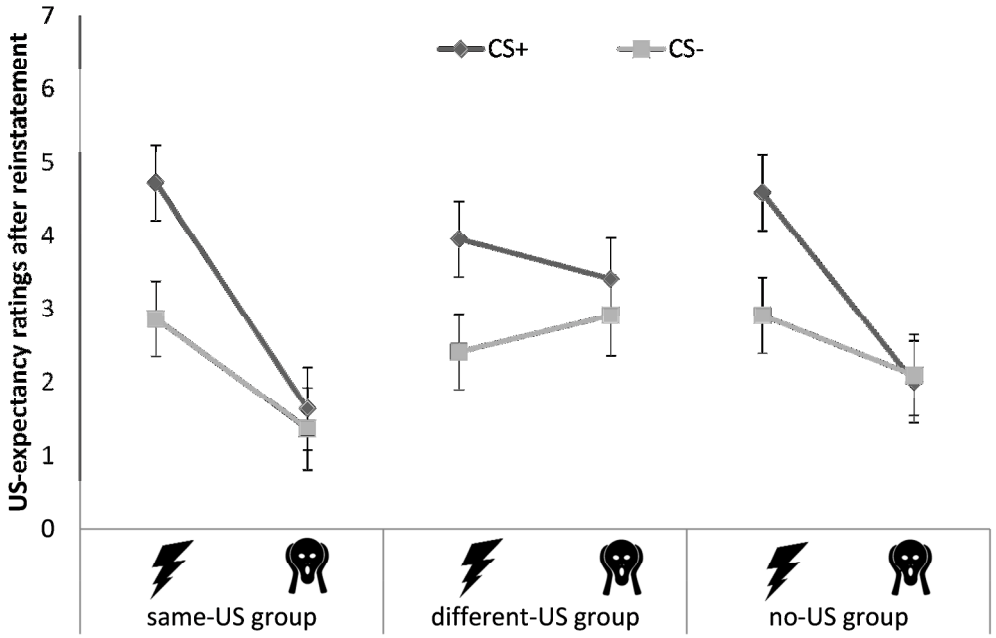
US-expectancy ratings after reinstatement
7
6
5
4
3
2
1
0
CS+
CS-
same-US group
different-US group
no-US group

Table 1. *Study design summary*

Group (*N*=66)	Practice	Habituation	Acquisition	Extinction	Reinstatement	Test
	2 x 8 trials	8 trials	3 x 8 trials (a1-3)	3 x 8 trials (e1-3)		1 x 8 trials
Same-US Group	8 x CS+	8 probes	12 x CS+	12 x CS+ only	2 x pain-US only	4 x CS+
(*n* = 22)	8 x CS-		12 x CS-	12 x CS-		4 x CS-
No-US Group	8 x CS+	8 probes	12 x CS+	12 x CS+ only	/	4 x CS+
(*n* = 22)	8 x CS-		12 x CS-	12 x CS-		4 x CS-
Different-US Group	8 x CS+	8 probes	12 x CS+	12 x CS+ only	2 x sound-US only	4 x CS+
(*n* = 22)	8 x CS-		12 x CS-	12 x CS-		4 x CS-

Note: CS = conditioned stimulus; US = unconditioned stimulus; pain-US = a painful electrocutaneous stimulus; sound-US = a non-painful, aversive human scream; CS+ = the movement that is followed by the pain-US during the acquisition phase; CS- = the movement that is never followed by the pain-US; pain-US only = unsignaled presentation of the pain-US; sound-US only = unsignaled presentation of the scream-US. During the extinction phase, the CS+ and CS- movements were never followed by any of the USs.

Table 2. *Descriptive statistics of the questionnaire scores and US characteristics for the three experimental groups*

	Mean (SD)				
	No-US Group	Same-US Group	Different-US Group	*F*	*p*
Age	20.91 (2.64)	21.59 (2.26)	23.59 (6.77)	2.22	.12
Self-reported pain-US intensity (1-10)	8.45 (0.51)	8.27 (0.55)	8.14 (0.77)	1.45	.24
Physical pain-US intensity (in mA)	32.36 (7.50)	32.09 (10.23)	36.91 (12.65)	1.51	.23
Painfulness of the sound-US (1-10)	4.86 (2.96)	4.45 (2.48)	3.55 (1.90)	1.62	.21
Unpleasantness of the sound-US (1-10)	6.09 (2.62)	5.86 (1.81)	5.91 (1.66)	0.07	.93
STAI-T	39.09 (8.57)	39.41(9.24)	40.09 (10.10)	0.07	.94
PCS	19.27 (9.08)	14.32 (8.77)	14.86 (8.62)	2.09	.13
PANAS –NA	21.86 (5.24)	20.82 (5.03)	21.36 (6.11)	0.20	.82
PANAS –PA	35.27 (4.68)	35.36 (4.57)	35.14 (6.30)	0.01	.99
FPQ	70.36 (14.87)	68.23 (13.70)	63.05 (16.01)	1.41	.25

Note: STAI -T= Trait portion of the State-Trait Anxiety Inventory; PCS = Pain Catastrophizing Scale; NA = Negative Affect Scale (PANAS = Positive and Negative Affect Schedule); PA = Positive Affect Scale (PANAS); FPQ = Fear of Pain Questionnaire; SD = standard deviation.